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DATE MAILED: 04/03/96

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☑ This application has been examined ☐ Responsive to communication filed on _____ ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☑ Notice of References Cited by Examiner, PTO-892.
2. ☑ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☑ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☑ Claims 1-34 are pending in the application.
   Of the above, claims 3-5, 13-18, 23, 25-28, 33-34 are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☑ Claims 1-2, 6-12, 19-22, 24, 29-32, 35-36 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____ ; filed on _____.
13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

1. Restriction to one of the following inventions is required under 35 U.S.C. 121:

Group I. Claims 1-2, 6-12, 19-22, 24, 29-32 and 35-36, drawn to DNA plasmids, packaging cell lines, and adenoviral vectors, classified in Class 435, subclass 320.1, for example.

Group II. Claims 3-9, 13-18, 23, and 25-31, drawn to DNA plasmids, packaging cell lines, and adeno-associated viral vectors, classified in Class 435, subclass 320.1, for example.

Group III. Claim 33, drawn to a method of treating a hereditary or acquired disease, classified in Class 514, subclass 44, for example.

Group IV. Claim 34, drawn to a vaccine, classified in Class 424, subclass 93.2, for example.

2. The inventions are distinct, each from the other because of the following reasons:

a. Inventions I and II are directed toward different types of vectors, and materials and methods for producing such vectors. The materials and methods required to produce adenoviral and adeno-associated viral vectors are distinct. In addition, the search required for each group is not co-extensive, especially with respect to the scientific literature.

b. Inventions I-II and III are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (M.P.E.P. § 806.05(h)). In the instant case, the vectors of Group I-II can be used for the *in vitro* production of protein with eukaryotic cells.

c. Inventions III and IV are disclosed as different combinations which are not connected in design, operation or effect. These combinations are independent if it can be shown that (1) they are not disclosed as capable of use together, (2) they have different modes of operation, (3) they have different functions, or (4) they have different effects. (MPEP 806.04, MPEP 808.01). In the instant case, Groups III and IV have different effects. The method of Group III results in the expression of a therapeutic gene which ameliorates a genetic disease. The vaccine of Group IV results in a protective immune response in an animal to prevent viral or bacterial infection.

d. The vectors of Group I-II and the vaccine of Group IV are distinct products capable of separate use. In the instant case, the vectors of Group I-II can be used in materially different processes including as cell culture expression vectors.

3. Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification, different search requirements and their recognized divergent subject matter, restriction for examination purposes as indicated is proper.

4. During a telephone conversation with Karen Krupen on 3/7/96, a provisional election was made with traverse to prosecute the invention of Group I, claims 1-2, 6-12, 19-22, 24, 29-32, and 35-36. Affirmation of this election must be made by applicant in responding to this Office action. Claims 3-5, 13-18, 23, 25-28, and 33-34 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b), as being drawn to a non-elected invention.

5. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 C.F.R. § 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a diligently-filed petition under 37 C.F.R. § 1.48(b) and by the fee required under 37 C.F.R. § 1.17(h).

6. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention and failing to adequately teach how to make and/or use the invention, i.e. failing to provide an enabling disclosure.

Applicants' invention is directed toward DNA plasmids and packaging cell lines for the production of adenoviral vectors. Plasmids, cell lines, and vectors are all claimed. Several examples are given which illustrate how to make the adenoviral vectors, Ad5/ΔE1ΔE4 and Ad5/ΔE1ΔE3, as well as the corresponding plasmids and packaging cell lines. However, the specification fails to enable the broad scope of applicants' claimed invention.

Specifically, the specification fails to enable the use a transcycline responsive promoter or all cAMP response element binding protein promoters to drive the expression of an adenoviral protein. Sequences, or directions to obtain sequences, for these inducible promoters have not been provided in the specification. Even if the gene sequences for these promoters were known at the time of the invention, applicants have failed to supply evidence which would indicate that these promoters would function effectively in 293 cells. Finally,

applicants have not enabled any and all combinations of deletions or mutations in the E1, E3, and E4 regions of an adenoviral vector. Applicants have only demonstrated that adenoviral vectors containing deletions in the E1 region combined with deletions in either the E3 or E4 region can be made using the disclosed techniques.

Consequently, the specification is non-enabled for the scope of the present claims.

7. Claims 1-2, 6-9, 11-12, 19-22, 24, 29-32, and 35-36 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

8. Claims 1-2, 6-9, and 31 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 1-2, 6-9, and 31 are vague and/or indefinite for the following reasons:

a. Claim 1 is vague due to the use of the phrase "gene region". It is not clear whether this term includes introns as well as exons, regulatory elements, or other DNA sequences which may be related to an adenoviral gene. Furthermore, it is not clear how many nucleotides must be present to be considered "a region".

b. Claim 6 is vague due to the use of the word "the" before "promoter" in line 2 of the claim. Since one would not expect that each promoter from the family of cAMP response element binding protein regulated genes is identical, it is recommended that the word "a" replace "the", unless, of course, there really is only one such promoter.

c. Claim 31 is vague since it is unclear what is encompassed by the term "slow-replicating" cells.

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

10. Claims 11-12, 19-22, 24, 29-31, and 35-36 are rejected under 35 U.S.C. § 102(a) as being clearly anticipated by Engelhardt et al [PNAS USA, 91:6196-6200 (1994)].

Engelhardt et al ("Engelhardt") disclose an adenovirus defective replication which contains deletions in the E1 region, E3 region, and the E2A region (see page 6196, last paragraph). Engelhardt teaches the packaging cell lines for propagation of the disclosed vectors on page 6197, paragraph 2. Mouse liver cells were

transfected with the adenoviral vectors containing a transgene (lacZ). Consequently, applicants' claims are clearly anticipated.

11. Claims 19-22 and 24 are rejected under 35 U.S.C. § 102(a) as being clearly anticipated by Armentano et al. [J. Cellular Biochemistry, 18:222 (1994)].

Armentano et al. ("Armentano") disclosed, in a symposium on gene therapy (January 15-22, 1994), an adenoviral vector containing a deletions in the E1, E3, and E4 regions. Consequently, applicants' claims are clearly anticipated.

12. The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

13. The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 86 S.Ct. 684, 15 L.Ed. 2nd 545 (1966), 148 USPQ 459, that are applied for

establishing a background for determining obviousness under 35 U.S.C. § 103 are summarized as follows:

1. Determining the scope and contents of the prior art;
2. Ascertaining the differences between the prior art and the claims at issue; and
3. Resolving the level of ordinary skill in the pertinent art.

14. Claims 1-2, 6-12, 19-22, 24, 29-32, and 35-36 are rejected under 35 U.S.C. § 103 as being unpatentable over Weinberg et al. [PNAS USA, 80:5383-5386 (1983)], Gregory et al [WO 94/12649], Su et al. [Biochemical and Biophysical Research Communications, 186(1):293-300 (1992)], and Pei et al. [Mol. Enocrinol., 5(4):521-534 (1991)].

Weinberg et al. ("Weinberg") disclose a cell line that supports the growth of adenovirus and adenoviral vectors defective in early region 4. The cell line, W162, was produced by stably transfecting these cells with a plasmid containing the E4 region of an adenoviral genome. Weinberg states that Vero cells (W162), rather than 293 cells (cells which complement E1 deletions), were chosen for these experiments for technical reasons and because E1-containing cell lines might activate the resident E4 DNA leading to cell death (see page 5386, discussion).

Su et al. ("Su") and Pei et al. ("Pei") disclose the gene sequence of the mouse α-inhibin promoter and teach that this inducible promoter contains several cAMP response elements.

Gregory et al. ("Gregory") teach methods for producing adenoviral vectors for gene therapy of cystic fibrosis. On page 55, lines 21-30, Gregory teaches that a cell line could be established which complements both an E1 and E4 deletion in an adenoviral vector. Specifically, Gregory states:

> A cell line could in theory be established that would fully complement E4 functions deleted from a recombinant virus. The problem with this approach is that E4 functions in the regulation of host cell protein synthesis and is therefore toxic to cells. The present recombinant adenoviruses are deleted for the E1 region and must be grown in 293 cells which complement E1 functions. The E4 promoter is activated by the E1a gene product, and therefore to prevent inadvertent toxic expression of E4 transcription of E4 must be tightly regulated. The requirements of such a promoter or transactivating system is that in the uninduced state expression must be low enough to avoid toxicity to the host cell, but in the induced state must be sufficiently activated to make enough E4 gene product to complement the E4 deleted virus during virus production.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to use the plasmid described by Weinberg, containing the promoter of Su and Pei, to stably transfect 293 cells thereby allowing for the production of E1/E4-deleted adenoviral vectors. One would have been motivated to use the promoter of Su and Pei since it was well known at the time the invention was made that promoters containing cAMP responsive elements inducibly regulated gene expression.

15. Any prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to D. Curtis Hogue, Jr. whose telephone number is (703) 308-1083. The examiner can normally be reached on Monday-Friday from 7:30 a.m. to 4:00 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jackie Stone, can be reached on (703) 308-3153. The fax phone number for this Group is (703) 308-4312.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

D. Curtis Hogue, Jr.

March 21, 1996

JACQUELINE M. STONE
SUPERVISORY PATENT EXAMINER
GROUP 1800